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PORTNER, VIRGINIA ALLEN

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/981,310	Applicant(s) Landegren et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 21, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6 and 8-10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1-6 and 8-10 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Withdrawn

2. Claims 1, 3,4 and 5 rejected under 35 U.S.C. 102(e) as being anticipated by Whiteley et al (US Pat. 5,962,223), in light of the claimed kits not comprising an immobilized reagent.

Rejections Maintained

3. Claims 1, 3 and 4 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record in paper number 24, paragraph 6.

4. Claims 1, 3 and 4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 24, paragraph 7.

5. Claims 1, 3, 4 and 5 rejected under 35 U.S.C. 102(b) as being anticipated by Landegren et al (US Pat. 4,988,617), for reasons of record in paper number 24, paragraph 9.

6. Claims 6, 8-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor et al (US Pat. 5,635,602; filing date 1993) in view of Suzuki et al (1995), for reasons of record in paper number 24, paragraph 12.

7. Claims 6, 8-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor et al (US Pat. 5,635,602; filing date 1993) in view of de la Monte et al (US Pat. 5,830,670; filing date May 1995), for reasons of record in paper number 24, paragraph 13.

8. Claims 1-5 rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor in view of de la Monte, for reasons of record in paper number 24, paragraph 14.

Response to Arguments

9. Applicant's arguments filed September 21, 2001 have been fully considered but they are not persuasive.

10. The rejection of claims 1, 3 and 4 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is argued by pointing the examiner to page 4, paragraph 5 of the instant specification.

11. The examiner upon consideration of the disclosure at the location asserted to provide support for the claimed invention, a kit that comprises three nucleic acid reagents or three co-factor

reagents for the determination of a protein, no original descriptive support could be found for three nucleic molecules that bind to a single protein antigen or three different co-factors that bind to a single protein.

While this section of the specification suggests the utilization of other "specifically interacting species with a known affinity", the specification does not teach that the antigen to which the combination of the three affinity reagents bind are three cofactors and or three nucleic acids that bind to a single protein antigen macromolecule. The claimed invention sets forth a genus of subspecies of invention not described in the instant specification for binding to a single protein analyte.

12. Applicant makes reference to a draft of a manuscript that utilizes two DNA aptamers and an antisera as the third affinity reagent.

13. It is the position of the examiner that this specific species of invention is not disclosed in the instant specification, and the combination of aptamers and an antisera is not described herein.

Applicant's arguments are not commensurate in scope with the claimed invention which is directed to the utilization of three affinity reagents that are all the same type of reagent for the detection of a protein antigen (i.e.: three nucleic acids, or three cofactors).

14. The rejection of claims 1, 3 and 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards

as the invention is traversed in light of the fact that it is possible for multiple nucleic acids and cofactors to have distinct binding sites on a protein.

15. It is the position of the examiner that platelet derived growth factor that has been exemplified in Applicant's arguments has been shown to interact with two nucleic acid molecules and not three nucleic acid molecules as now claimed.

The assay data provided is not commensurate in scope with the claimed invention which is directed to a kit that comprises three nucleic acids or three cofactors for a single protein that can be used to specifically detect a protein antigen.

No proteins that bind to three nucleic acids or to three co-factors have been described, what the three nucleic acids or three co-factors are that will bind to a single protein analyte macromolecule simultaneously has not been defined in the instant specification, thus the invention is not clearly or distinctly claimed.

16. The rejection of claims 1, 3, 4 and 5 under 35 U.S.C. 102(b) as being anticipated by Landegren et al (US Pat. 4,988,617) is traversed and asserted that the macromolecule detected by Landegren et al is a nucleic acid and the method steps of the prior art differ from the methods steps of the instant Application.

17. It is the position of the examiner that the instantly claimed invention is directed to a kit composition, and not a method. The reagents in the kit may be used for any purpose. The prior art was applied to the claims because the prior art kits comprised the same or equivalent reagents

as the those claimed in claims 1, and 3-5. The instantly claimed kits are directed to kits that comprise three nucleic acid molecules that can bind to a macromolecule, wherein two of the nucleic acid molecules are amplifiable to generate a detectable signal. Landegren (prior art, see claim 20-28)) claims kits that comprise first, second and third nucleic acid molecules that will bind to the same macromolecule, wherein two of the nucleic acid molecules are amplifiable (col. 2, lines 50 and claim 21) .

The instantly claimed kits comprise nucleic acids of any sequence as long as all three nucleic acids are affinity reagents that can bind to the same specific macromolecule simultaneously, two of the three must be modified with amplifiable oligonucleotides and one must be immobilized.

The claim limitation "is a protein", does not define three specific nucleic acid affinity reagents and therefore is being read as an intended use of the kit, which does not define over the applied prior art. The kits of the prior art contain the same or equivalent reagents as the instantly claimed kits, three nucleic acid molecules that have binding affinity for a macromolecule, together with ligase (col. 2, line 50; claim 21).

18. The reagents of Landegren are asserted to not comprise two separate parts, the first being that part that specifically binds to the analyte and the second part that is an oligonucleotide that modifies the first part and that is conjugatable.

19. It is the position of the examiner that the affinity regents of Landegren '617 comprise oligonucleotides that specifically bind to the analyte, and the second part that is an oligonucleotide that modifies the first part and that is conjugatable. The ligation of the second affinity reagent to the third affinity reagent by ligase results in the generation of a detectable signal. Each of the affinity reagents can be considered to comprise a specific binding portion and an amplifiable portion, wherein each end of the second and third reagents are amplified upon the action of ligase when they are bound to the desired analyte macromolecule (see '617, Figure 1). A signal is only generated when the second and third affinity reagents are closely bound to one another on the same macromolecule and amplified through the action of ligase.

The rejection is maintained for reasons of record in paper number 24.

20. The rejection of claims 6, 8-10 under 35 U.S.C. 103(a) as being unpatentable over Cantor et al (US Pat. 5,635,602; filing date 1993) in view of Suzuki et al (1995) is traversed by asserting that "Cantor et al disclose an assay where two reagents with affinity for a target protein are connected via double stranded DNA sequence when they are added to a sample" and in the present invention "the second and third affinity reagents are connected to a single DNA strand and are separately added to the immobilized target molecule."

21. Upon consideration of the traversal relative to the recited claim language of claim 6, the claimed second and third antibodies must be modified with conjugatable oligonucleotides which must have the ability of being conjugatable one to the other when they are bound to the detected

antigen. The second and third antibodies of Cantor are first conjugated with oligonucleotides (see Figure 8). The oligonucleotides are single stranded nucleic acid molecules (DNA). The second and third antibodies comprise an oligonucleotide sequence that is conjugate able one to the other and are incubated with the antigen sample (see col. 34, lines 52-53).

The method of Cantor digests the linker DNA molecule of the bis(Fab')-DNA conjugate after the second and third affinity reagents bind to their respective epitopes (see col. 34, lines 14-18). The linker DNA is removed from the sample (see col. 34, line 19) if the antibodies are not bound to epitopes close to one another. Religation only occurs when the second and third affinity reagents bind to epitopes that are close to one another on the macromolecule (see col. 34, lines 19-21). Antibodies that bound to epitopes close to one another are modified with conjugatable oligonucleotides when they are religated (see col. 34, lines 24-28). Amplification of the ligated oligonucleotides is carried out by PCR (see col. 34, lines 28-30). The amplified products are detected (see col. 34, lines 30-55).

It is the position of the examiner that Cantor teaches an immunoassay method that utilizes antibodies modified with conjugatable oligonucleotides, and the method comprises the steps of contacting antigen with a solid support(col. 33, lines 62-65), washing(col. 33, line 65), incubating (col.34, lines 5-7), washing (col. 34, line 8), amplifying (col. 34, 29) and detecting the amplified products (col. 34, line 32-38 and lines 52-55).

Applicant's arguments directed to the separate addition of the second and third affinity reagents is not commensurate in scope with the claimed invention. The claimed invention does not

require the second and third affinity reagents to be added separately. The method of claim 6 requires "incubating with a solution of a second and a third antibody specific for a second and a third epitope of said antigen." The claimed method does not require that the second and third reagents be added separately, as asserted by Applicant.

The functional language recited in the claims only requires the affinity reagents to be modified with oligonucleotides, and to be capable of being conjugated one to the other only when they are closely bound on the macromolecule. Cantor teaches this capability. The oligonucleotides are digested and religated only when they are closely bound on the macromolecule.

The claim recites open language which permits that additional methods steps of Cantor that insure that the affinity reagents are conjugatable to one another only when they are bound to epitopes close to one another. Cantor teaches that conjugation of the second and third affinity reagents after they bind to antigen (col. 34, lines 28-30 and 52-55).

22. Applicant asserts the advantages of reduced background and specific signal amplification not taught by Cantor et al.

23. It is the position of the examiner that Cantor et al teach washing steps for the removal of unbound reagents to reduce background, as well as the amplification of the religated DNA reduces noise background (see col. 34, line 39). Detection of the amplified full length PCR product is readily determined and provides for increased ease of detecting the amplified product

(see col. 34, lines 43-51). The advantages asserted to be true of the instantly claimed method are also taught by Cantor (see col. 34, lines 38-51).

24. Cantor et al is asserted to evidence increased background due to non-specific binding events from the connected protein becoming immobilized even if there is not correct target determinant.

25. It is the position of the examiner that the method of Cantor reduces non-specific binding.

The "connected protein" is digested with a restriction endonuclease to digest the DNA linker, and then washed (see col. 34, lines 12-19). This process reduces background. When binding only occurs to a single antigen(epitope), or not at all, the non-binding affinity reagents are washed away with extensive washing (col. 34, line 17).

26. Applicant asserts data presented in the attached manuscript in Figure 4 show an assay with increased, unexpected and improved sensitivity.

27. It is the position of the examiner that Figure 4 is not disclosed in the instant specification. The reagents used are not described in the instant specification. The method of instant claim 6 does not require a connector oligonucleotide sequence which was used to produce the graph shown in the attached manuscript, Figure 4. Applicant's arguments are not commensurate in scope with the claimed invention.

28. It is asserted by Applicant that Suzuki et al or de la Monte et al do not suggest the modification of Cantor et al so to achieve the present invention or the advantages associated with the present invention.

29. It is the position of the examiner that both Cantor and Suzuki are directed to the use of immuno-polymerase chain reaction immunoassays that utilize antibodies that are modified with conjugatable oligonucleic acids, and Suzuki teaches that through sandwiching an antigen between an immobilized first antibody and an antibody that is modified with an amplifiable label, an immunoassay with a thousand fold more sensitivity can be obtained, and Suzuki teaches that the immunoassay can be readily applied to any antigen-antibody system to which monoclonal antibodies are available. Suzuki et al clearly suggests the modification of immunoPCR assays with of an immobilizing antibody to achieve greatly enhanced assay results. The prior art clearly suggests the modification of immuno-PCR assays with an immobilizing antibody for the attainment of improved test results. Cantor et al teach macro molecules that present at least three epitopes (col. 10, lines 1-10), and the importance of detecting macro molecules that present pairs of epitopes in order to provide discriminating accurate analysis, where the application of an individual monoclonal antibody is insufficient for accurate analysis (see Cantor: see col. 9, lines 58 through col. 10, line 10; col. 34, lines 52-55).

30. The method of Suzuki et al is discussed with specific assay format features and the instant invention is argued to comprise different affinity reagents.

31. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

32. The rejection of claims 6, 8-10 under 35 U.S.C. 103(a) as being unpatentable over Cantor et al (US Pat. 5,635,602; filing date 1993) in view of de la Monte et al (US Pat. 5,830,670; filing date May 1995) is asserted not to be able to achieve the present invention, the disclosure of de la Monte is directed to a particular class of proteins associated with Alzheimer's disease, that the assay is a conventional sandwich ELISA and not nucleic acid conjugation or amplification is disclosed.

33. It is the position of the examiner that de la Monte does teach the utilization of nucleic acid conjugation and amplification (see claim 6, immunopolymerase chain reaction (immuno-PCR)) in the detection of a protein antigen. The antigen of de la Monte is a protein antigen, which reads on the antigen of the instant invention. The immunoassay of de la Monte teaches the immobilization of an antibody specific for a protein antigen (de la Monte, claim 4) and detection of the antigen utilizing immuno-PCR (de la Monte, claim 6).

The combination of reagents, and the methods steps carried out by de la Monte do not define a conventional ELISA, because a plurality of antibodies are utilized which are directed to different epitopes and immunoPCR is used in the process of detection of the antigen.

de la Monte was cited to show the immobilization of an antibody on the solid phase in an immunoPCR method defines a methods step that results in the diagnosis of a human disease. de la Monte teaches that through sandwiching an antigen between immobilized antibodies and antibodies specific to multiple epitopes directed to a diagnostic antigen, it is possible to diagnose the presence of a disease associated antigen through specific binding of antibodies to a plurality of epitopes (de la Monte, see claim 1). Cantor et al teach macro molecules that present at least three epitopes (see Cantor, col. 10, line 7), and the importance of using an immunoassay that detects the presence of pairs of epitopes on macro molecules in order to provide discriminating accurate analysis where the application of an individual monoclonal antibody is insufficient for accurate analysis (see Cantor: see col. 9, lines 58 through col. 10, line 10; col. 34, lines 52-55).

34. It is asserted that the method of de la Monte et al would have the same background problems discussed with respect to Suzuki et al and Cantor et al.

35. It is the position of the examiner that Cantor et al provide guidance and teaching for the reduction of background in an immuno-polymerase chain reaction assay through the re-ligation of conjugated antibodies and amplification of only those oligonucleotides attached to modified antibodies that are bound to antigens that are close to one another. de la Monte et al was not cited for teaching the instantly claimed method, but for what the reference teaches with respect to utilization of an immobilized antibody on the solid support in an immuno-PCR immunoassay for

detection of a protein macromolecular antigen with multiple antibodies directed against different epitopes on the protein.

36. Specific arguments directed to the rejection of claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Cantor in view of de la Monte were not specifically addressed but argued with respect to claims 6 and 8-10. Both rejections under 35 U.S.C. 103 (a) over Cantor in view of de la Monte are maintained in view of Cantor teaching the claimed method all but the immobilization of an antibody on the solid phase in an immunoPCR assay and de la Monte et al teach the utilization of an immobilized antibody in an immunoPCR assay provides means for detecting the presence of a protein antigen correlated with diagnosis of a human disease.

37. In the absence of a showing of unexpected results, the applied references obviate the now claimed invention.

Conclusion

38. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

39. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
January 14, 2002

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